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Health and Environmental Effects Profile for Phthalic Anhydride

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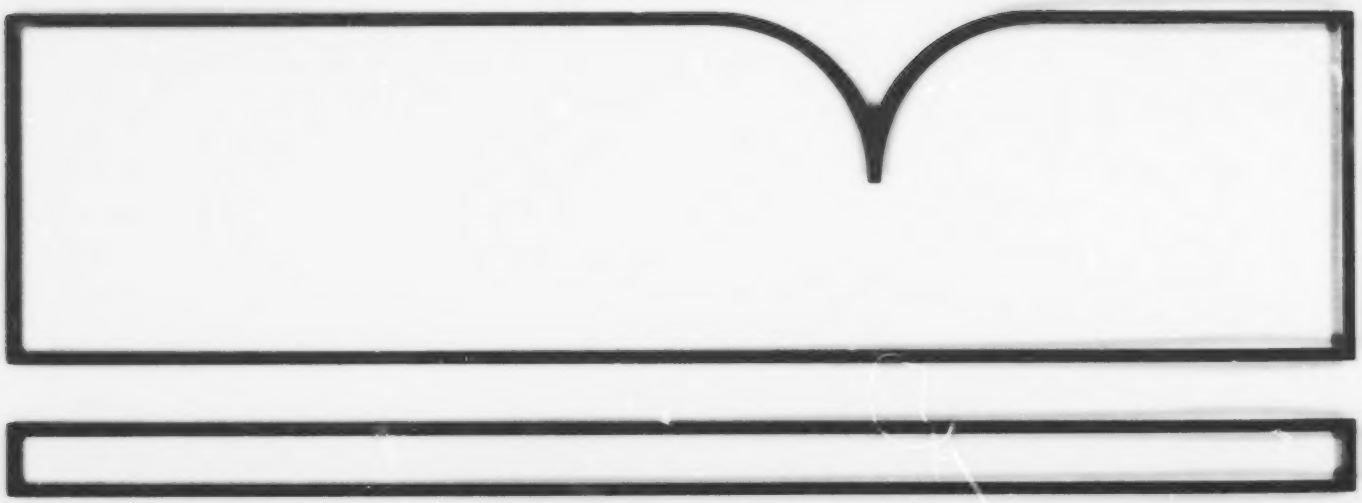

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16. ABSTRACT

The Health and Environmental Effects Profile for Phthalic Anhydride was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Phthalic anhydride has been determined to be a systemic toxicant. A Reference Dose (RfD), defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effect during a lifetime, for phthalic anhydride is 7.5 mg/kg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for phthalic anhydride is 1000.

17. KEY WORDS AND DOCUMENT ANALYSIS

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

Phthalic anhydride is a white solid at ambient temperature, with a characteristic choking odor (Verschueren, 1983). It is slightly soluble in water at room temperature and is soluble in pyridine (Bemis et al., 1982). In 1984, six U.S. companies at eight locations produced this chemical (SRI, 1985). The U.S. production of phthalic anhydride in 1984 was 870.2 million pounds (USITC, 1985). About 94% of U.S. production facilities use the o-xylene oxidation process for the production of phthalic anhydride (SRI, 1985). About 53% of the phthalic anhydride produced in the United States is used as plasticizers, 22% for the manufacture of polyester resins, 19% for alkyd resins and 6% for miscellaneous uses (CMR, 1983).

In water, phthalic anhydride hydrolyzes to phthalic acid with an estimated half-life of 1.5 minutes (Hawkins, 1975). Phthalic anhydride is expected to be readily biodegradable under wastewater treatment conditions (Matsui et al., 1975; Sasaki, 1978). The biodegradability of phthalic acid, the hydrolysis product of phthalic anhydride, was studied with a river die-away test. With Mississippi River water, the estimated biodegradation half-life was 1.5 weeks. Phthalic anhydride is not expected to bioaccumulate in aquatic organisms (Lu and Metcalf, 1975; Kenaga, 1980). From the estimated Henry's Law Constant (Singh et al., 1984), it is expected that the compound will not volatilize from water. From its estimated K_{oc} and measured water solubility (Kenaga, 1980), it is predicted that significant removal from water media through sedimentation of particulate-sorbed compound will not occur.

Pertinent data regarding the fate and transport of this compound in the atmosphere could not be located in the available literature as cited in the Appendix. From the estimated OH radical reaction rate constant (Singh et al., 1984), its atmospheric half-life that is due to this reaction has been estimated to be ~16 hours. Based on the probability of adsorption of vapor-phase phthalic anhydride to atmospheric particulate matter (Cupitt, 1980), it is predicted that removal of atmospheric phthalic anhydride through deposition of air particulate matter is not likely to be significant. Wet deposition may, however, remove some of the atmospheric compound.

The fate and transport of phthalic anhydride in soil has been predicted from its expected or known behavior in water. In moist soil, the compound will hydrolyze rapidly to phthalic acid. Biodegradation of phthalic acid is expected to be a major fate process in soil. Phthalic anhydride is not expected to be transported from soil to the atmosphere through volatilization. With the exception of soil contaminated by accidental spills or waste disposal, the compound is not likely to be transported to groundwater through leaching.

Phthalic anhydride was identified in effluents from two unspecified chemical plants in the United States (Shackelford and Keith, 1976). It was also detected in several drinking waters in the United States, although no concentrations were reported (Shackelford and Keith, 1976; Kool et al., 1982; Deinzer et al., 1975). It was also identified in 1 of 14 treated water samples in England (Fielding et al., 1981).

The only reported presence of phthalic anhydride in the atmosphere was in an arctic aerosol at a concentration of ~10 mg/m^3 (Weschler, 1981); however, the author noted that phthalic anhydride most likely originated from the partial hydrolysis of phthalate esters followed by dehydration in the GC injection port.

Coleman et al. (1981) detected phthalic anhydride in the volatile flavor components of baked Idaho potatoes by MS and IR spectral identification.

Pertinent data regarding dermal exposure to phthalic anhydride could not be located in the available literature as cited in the Appendix.

Little information is available concerning the toxicity of phthalic anhydride to aquatic organisms. Fathead minnows and sea lampreys were unaffected by acute exposures to 56 and 5 mg/ℓ, respectively (Applegate et al., 1957; Pickering and Henderson, 1966). Two laboratory microecosystem studies (Lu and Metcalf, 1975; Soedergren, 1982) indicated that phthalic anhydride was not accumulated to a great extent in organisms exposed to phthalic anhydride itself or di-2-ethylhexyl phthalate.

Dixon et al. (1978) reported that covalently bound radioactivity was found in all tissues of fetuses CD-1 of mouse dams injected intraperitoneally with 80 mg/kg ^{14}C-phthalic anhydride on days 11, 12 and 13 of gestation. No other data regarding the pharmacokinetics or metabolism of phthalic anhydride could be located in the available literature as cited in the Appendix.

The NCI (1979) found phthalic anhydride to be noncarcinogenic based upon a 2-year bioassay in which F344 rats and B6C3F1 mice were exposed to dietary levels up to 15,000 ppm (rats) or 33,000 ppm (mice).

Phthalic anhydride was negative for reverse mutations in several strains of Salmonella typhimurium mutation assays with or without metabolic activation (Florin et al., 1980; Zeiger et al., 1985; Shelby and Stasiewicz, 1984), mammalian cell culture (Shelby and Stasiewicz, 1984) and for chromosome aberrations or sister chromatid exchanges in mammalian cell culture (Shelby and Stasiewicz, 1984). Intraperitoneal injections in gravid mice,

at doses as low as 55.5 mg/kg, have been reported to produce fetal abnormalities (Brown et al., 1978). An intraperitoneal dose of ~203 mg/kg/day on gestation days 8-10 in CD-1 mice produced major, but unspecified, malformations in 50% of all fetuses (Fabro et al., 1982). Korhonen et al. (1983) found phthalic anhydride to be embryotoxic in chicken eggs. Protsenko (1970) cited reproductive defects in rats exposed to as little as 0.2 mg/m³ phthalic anhydride.

In the NCI (1979) bioassay, male rats exposed to 15,000 ppm dietary phthalic anhydride for 2 years showed a minor inhibition in weight gain, relative to untreated controls. Treated rats of both sexes also had low incidences of arched back, rough hair coat, ulceration and corneal opacity, although it was unclear if these effects were concentrated-related. Treatment of male mice with 16,346 or 32,694 ppm and of female mice with 12,019 or 24,038 ppm led to more severe and concentration-related inhibitions in weight gain. Low- or high-dose female and male mice had significantly increased incidences of lung and kidney lymphocytosis. High-dose male and female mice had significantly increased incidences of chronic bile duct inflammation, and low- and high-dose male had dose-related, significantly increased incidences of adrenal atrophy and mineralization of the thalamus. In a 7-week study designed to determine an MTD for the chronic experiment, the NCI (1979) noted severe inhibition in weight gain in male and female rats given 50,000 ppm phthalic anhydride, and hepatocytic cytoplasmic vacuolation in male rats fed 25,000 ppm. At 50,000 ppm, hepatic toxicity was not found in either rats or mice.

Studies of occupational exposure to phthalic anhydride powder have revealed asthmatic attacks and mucous membrane irritation of the eyes, lungs and skin (Markman and Savinkina, 1964; Ohta et al., 1979). Ohta et al.

(1979) reported that factory workers exposed to air concentrations of phthalic anhydride dust ranging from 24.9-77.3 ppm (151-468 mg/m³) had high incidences of respiratory and eye symptoms than workers exposed to ≤1.1 ppm (6.7 mg/m³). In six workers employed an average of 6.6 years in a phthalic anhydride plant, normal neuromuscular activity was observed, with the exception of one worker who suffered from a bilateral Achilles hyporeflexia (Gilioli et al., 1978). The asthma-inducing and hypersensitivity characteristics of phthalic anhydride have been determined by a number of investigators (Maccia et al., 1976; Fawcett et al., 1977; Bernstein et al., 1982, 1984), who have observed specific antibody binding against the compound.

Sensitization to phthalic anhydride has also been demonstrated in experimental animals (Jacobs et al., 1940; Chernichenko et al., 1973). Zhilova and Kasparov (1968) stated, however, that oral exposure did not induce the sensitizing and irritancy effects observed after other routes of exposure.

A provisional RfD of 7.5 mg/kg/day or 525 mg/day for a 70 kg human was recommended. The RfD was based on a chronic rat NOAEL of 750 mg/kg/day (15,000 ppm in the diet) in the NCI (1979) study using an uncertainty factor of 100. Higher doses (≥1562 mg/kg/day) in mice resulted in dose-related decreased body weight gain and dose-related increased incidences of histopathological lesions in lung, kidney, bile duct and adrenals. The RfD was considered provisional because phthalic anhydride has not been adequately tested for teratogenicity or male reproductive effects by the oral route.

An RQ of 1000 was based on the study by Ohta et al. (1979), in which occupational exposure was associated with bronchial asthma.

Because negative results for carcinogenicity were obtained in a 2-year dietary study in rats and mice (NCI, 1979), phthalic anhydride is an IARC Group 3 and a CAG Group E chemical (U.S. EPA, 1984); meaning that the compound is not a carcinogen and other criteria must be used to rank phthalic anhydride for a reportable quantity under CERCLA. Should additional data for carcinogenicity or genotoxicity become available, the weight of evidence classification of Group E will be reconsidered.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
BODT	Biochemical oxygen demand, theoretical
CAS	Chemical Abstracts Service
COD	Chemical oxygen demand
CS	Composite score
DMSO	Dimethyl sulfoxide
ED_{50}	Effective dose to 50% of recipients
E_tOH	Ethanol
GC	Gas chromatography
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IR	Infrared
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
MS	Mass spectral
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RfD	Reference Dose
RQ	Reportable quantity

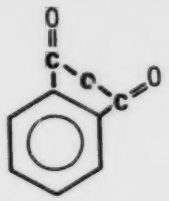
LIST OF ABBREVIATIONS (cont.)

RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term exposed level
tD_{50}	Dose that produces major malformations in 50% of fetuses
TLV	Threshold limit value
TWA	Time-weighted average
v/v	Volume per volume

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The chemical commonly known as phthalic anhydride is also known as 1,2-benzenedicarboxylic acid anhydride; 1,3-dihydro-1,3-dioxoisobenzofuran-phthalandione; and 1,3-phthalandione. This compound is also known by the tradenames Retarder ESEN®, Retarder AK® and Retarder PD® (U.S. EPA, 1985). The structure, empirical formula, molecular weight and CAS Registry number for phthalic anhydride are as follows:



Empirical formula: $C_8H_4O_3$

Molecular weight: 148.12

CAS Registry number: 85-44-9

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Phthalic anhydride is a white solid at ambient temperature with a characteristic odor and with a choking quality (Verschueren, 1983). It is slightly soluble in water at room temperature but more soluble in pyridine (Bemis et al., 1982). Other physical properties of phthalic anhydride are listed below:

Melting point:	131°C	Bemis et al., 1982
Boiling point:	284.5°C (sublimes)	Bemis et al., 1982
Specific gravity at 4°C:	1527	Bemis et al., 1982
Vapor pressure at 25°C:	5.8×10^{-4} mm Hg (extrapolated values)	Jones, 1960
	5.1×10^{-4} mm Hg	Amoore and Hautala, 1983
	5.2×10^{-4} mm Hg	Singh et al., 1984

Solubility in water at 25°C:	6200 mg/ℓ 6220 mg/ℓ 6000 mg/ℓ	Kenaga, 1980 Singh et al., 1984 Bemis et al., 1982
Henry's Law Constant at 25°C:	1.6×10^{-8} atmos·m³mol^{-1}	Singh et al., 1984
Log K_{ow}:	-0.62	Hansch and Leo, 1985
K_{oc}:	36 (estimated)	Kenaga, 1980
Air odor threshold (ppm; v/v):	0.053	Amoore and Hautala, 1983
Conversion factor at 20°C:	1 ppm = 6.06 mg/m³	Bemis et al., 1982

Phthalic anhydride reacts with monofunctional alcohols at elevated temperatures or at low moderate temperatures in the presence of a catalyst to yield esters that are used as plasticizers. It also reacts with polyfunctional alcohols to yield polyester polymers. Both of these reactions are commercially important. Phthalic anhydride also hydrolyzes in water.

1.3. PRODUCTION DATA

Table 1-1 lists annual production capacities of U.S. companies manufacturing phthalic anhydride as of January, 1985.

SRI (1985) reported that Koppers Co., Inc., Bridgeville, PA, was scheduled to shut down following the restart of the company's plant at Cicero, IL, during the second quarter of 1985 (SRI, 1985).

The U.S. production volume of phthalic anhydride in 1984 was 870.2 million pounds (USITC, 1985). Phthalic anhydride is manufactured by vapor phase oxidation of naphthalene or o-xylene in the presence of a catalyst with excess air in either fixed or fluid bed converters. In the fluid bed process, the finely divided catalyst is suspended in the moving feed stock and air, which causes it to behave like a fluid. Vanadium oxide on silica gel is generally used as the catalyst for this process (Fawcett, 1970; Bemis

TABLE 1-1

Manufacturers of Phthalic Anhydride in the United States*

Company	Location	Annual Capacity (millions of pounds)
Badische Corp.	Kearny, NJ	175
Exxon Corp.	Baton Rouge, LA	220
Koppers Co., Inc.	Bridgeville, PA	90
	Cicero, IL	235
Monsanto Co.	Texas City, TX	165
	Bridgeport, NJ	80
Stepan Co.	Millsdale, IL	170
Tenn-USS Chemical Co.	Pasadena, TX	210
	TOTAL	1345

*Source: SRI, 1985; USITC, 1985

et al., 1982). In the fixed bed process, vanadium oxide-titanium dioxide coated on an inert, nonporous fixed carrier acts as the catalyst. With the phasing out of the Koppers Co., Inc., Bridgeville, PA, facility, which used the naphthalene oxidation process, ~94% of U.S. production facilities use o-xylene oxidation process for the production of phthalic anhydride (SRI, 1985). Refined phthalic anhydride is stored molten for shipment in tank cars or tank trucks, or the solid product is packaged as a flake in multi-walled bags (Fawcett, 1970; Bemis et al., 1982). Typical specifications for commercial phthalic anhydride are as follows (Bemis et al., 1982):

Phthalic anhydride:	99.0% (minimum)
Phthalic acid:	0.1% (maximum)
Maleic acid:	0.3% (maximum)
Benzoic acid:	0.1% (maximum)
Naphthaquinine (if manufactured from naphthalene):	0.0002% (maximum)

1.4. USE DATA

According to CMR (1983), 53% of phthalic anhydride produced in the United States is used as plasticizers, 22% for the manufacture of polyester resins, 19% for alkyd resins and 6% for miscellaneous uses. The miscellaneous uses of phthalic anhydride include its export and use as an intermediate in the manufacture of dyes, saecharin, flame retardants, pesticides and other chemicals (Bemis et al., 1982).

1.5. SUMMARY

Phthalic anhydride is a white solid at ambient temperature, with a characteristic choking odor (Verschueren, 1983). It is slightly soluble in water at room temperature and is soluble in pyridine (Bemis et al., 1982). In 1984, six U.S. companies at eight locations produced this chemical (SRI, 1985). The U.S. production of phthalic anhydride in 1984 was 870.2 million pounds (USITC, 1985). About 94% of U.S. production facilities use the

o-xylene oxidation process for the production of phthalic anhydride (SRI, 1985). About 53% of the phthalic anhydride produced in the United States is used as plasticizers, 22% for the manufacture of polyester resins, 19% for alkyd resins and 6% for miscellaneous uses (CMR, 1983).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

Two processes that may significantly degrade phthalic anhydride in water are hydrolysis and biodegradation. The hydrolysis of phthalic anhydride at different pHs was studied by Hawkins (1975). The rate constant for the forward reaction in aqueous solution at 25°C was determined to be 7.9×10^{-3} sec^{-1}. Based on this rate constant, the half-life for hydrolysis has been estimated to be ~1.5 minutes. Therefore, phthalic anhydride is likely to hydrolyze rapidly in water forming phthalic acid. The biodegradation potential for phthalic anhydride was studied by various investigators. Heukelkian and Rand (1955) reported that between 44 and 78% (based on the BODT) of the compound mineralized in 5 days as a result of incubation of 1-4 mg/ℓ of the compound with sewage as microbial inoculum. Takemoto et al. (1981), on the other hand, observed only ~21% degradation of an initial concentration of 2 mg/ℓ after incubation with sewage for 5 days by the standard dilution method; the observed degradation was even slower (18%) with the seawater dilution method. Matsui et al. (1975) used activated sludge as the microbial inoculum and reported 33% degradation of an initial concentration of 9 mg/ℓ phthalic anhydride in 24 hours (based on COD removal). Using the Japanese MITI test (100 mg/ℓ test substance incubated with active sludge at 25°C at a pH of 7 for 2 weeks), Sasaki (1978) determined that phthalic anhydride was "well-biodegradable," meaning >30% of the compound degraded after 2 weeks. Saeger and Tucker (1973) studied the biodegradability of phthalic acid (hydrolysis product of phthalic anhydride) with a river die-away test (Mississippi River) and estimated a biodegradation half-life of 1.5 weeks.

The fate of phthalic anhydride was also studied by Lu and Metcalf (1975) in a model aquatic ecosystem. Phthalic anhydride was almost completely converted to phthalic acid. The compound was found not to bioaccumulate in mosquito fish, Gambusia affinis. Using a regression equation, Kenaga (1980) predicted a BCF value of 5 for phthalic anhydride in aquatic organisms. Therefore, this compound is not expected to bioaccumulate in aquatic organisms.

Pertinent data regarding the transport of phthalic anhydride in water could not be located in the available literature as cited in the Appendix; however, from the estimated Henry's Law Constant of 1.6×10^{-8} atmos·m^3 mol^{-1} (Singh et al., 1984) and the volatility characteristics associated with various ranges of Henry's Law Constant, as given by Lyman et al. (1982), this compound is not expected to volatilize from water. Similarly, from the low K_{oc} of 36 (Kenaga, 1980) and the water solubility of 6200 mg/ℓ (Kenaga, 1980), it is predicted that at low concentrations the compound will not be significantly removed through sedimentation in water.

2.2. AIR

Singh et al. (1984) estimated the rate constant for OH radical reaction with phthalic anhydride to be 1.2×10^{-11} cm^3 molecule^{-1} sec^{-1}. Based on this value and assuming the concentration of OH radical in the atmosphere to be 10^6 molecule cm^{-3} (Cupitt, 1980), it is estimated that the atmospheric half-life for this reaction will be ~16 hours. Cupitt (1980) reported that adsorption may be a reasonable vaporphase removal mechanism only for chemicals with vapor pressures $\leq 10^{-7}$ mm Hg. Since the vapor pressure of phthalic anhydride is ~10^{-4} mm Hg at 25°C (see Section 1.2.), removal of atmospheric phthalic anhydride through deposition of particle-sorbed phthalic anhydride is not expected to be significant. The atmospheric moisture, however, is likely to convert substantial amounts of

phthalic anhydride into phthalic acid, which may reduce the probability of phthalic anhydride removal through wet deposition since the water solubility of phthalic anhydride is greater than the corresponding acid (Verschueren, 1983).

2.3. SOIL

Pertinent data regarding the fate and transport of phthalic anhydride in soil could not be located in the available literature as cited in the Appendix. Based on its physicochemical properties and behavior in water, some predictions about its fate and transport in soil can be made. Since the compound is susceptible to rapid hydrolysis (see Section 2.1.), phthalic anhydride will hydrolyze to phthalic acid in moist soils. Because the compound is easily biodegraded in water (see Section 2.1.), it is anticipated that biodegradation will be a major fate process for this compound in soil, as well.

Based on its estimated volatility from water (see Section 2.1.), it seems unlikely that volatilization will play a significant role in determining the transport of phthalic anhydride from soil to the atmosphere. In moist soils, hydrolysis of phthalic anhydride to phthalic acid is expected to decrease the mobility of the compound because of the lower aqueous solubility of phthalic acid compared with phthalic anhydride. This retardation of soil mobility may enhance the biodegradation potential of the compound. The probability of groundwater contamination by phthalic acid from soil leaching depends on two competitive processes. Assuming that biodegradation is the fastest degradation process and that the rate of biodegradation in soil is faster than its rate of leaching, the compound will not contaminate groundwater; however, the dumping of large quantities of phthalic anhydride in soil, as in the case of accidental spills or waste disposal sites, enhances the probability of soil leaching.

2.4. SUMMARY

In water, phthalic anhydride hydrolyzes to phthalic acid with an estimated half-life of 1.5 minutes (Hawkins, 1975). Phthalic anhydride is expected to be readily biodegradable under wastewater treatment conditions (Matsui et al., 1975; Sasaki, 1978). The biodegradability of phthalic acid, the hydrolysis product of phthalic anhydride, was studied with a river die-away test. With Mississippi River water, the estimated biodegradation half-life was 1.5 weeks. Phthalic anhydride is not expected to bioaccumulate in aquatic organisms (Lu and Metcalf, 1975; Kenaga, 1980). From the estimated Henry's Law Constant (Singh et al., 1984), it is expected that the compound will not volatilize from water. From its estimated K_{oc} and measured water solubility (Kenaga, 1980), it is predicted that significant removal from water media through sedimentation of particulate-sorbed compound will not occur.

Pertinent data regarding the fate and transport of this compound in the atmosphere could not be located in the available literature as cited in the Appendix. From the estimated OH radical reaction rate constant (Singh et al., 1984), its atmospheric half-life that is due to this reaction has been estimated to be ~16 hours. Based on the probability of adsorption of vapor-phase phthalic anhydride to atmospheric particulate matter (Cupitt, 1980), it is predicted that removal of atmospheric phthalic anhydride through deposition of air particulate matter is not likely to be significant. Wet deposition may, however, remove some of the atmospheric compound.

The fate and transport of phthalic anhydride in soil has been predicted from its expected or known behavior in water. In moist soil, the compound will hydrolyze rapidly to phthalic acid. Biodegradation of phthalic acid is expected to be a major fate process in soil. Phthalic anhydride is not

cted to be transported from soil to the atmosphere through volatiliza-
. With the exception of soil contaminated by accidental spills or waste
posal, the compound is not likely to be transpc.ted to groundwater
ugh leaching.

3. EXPOSURE

3.1. WATER

Phthalic anhydride was reported to be present in effluents from two unspecified chemical plants (Shackelford and Keith, 1976). It was also detected in drinking water, although the source of the waters and the concentrations of phthalic anhydride were not specified (Shackelford and Keith, 1976). Kool et al. (1982) qualitatively reported the presence of phthalic anhydride in U.S. drinking water. Using a cellulose acetate reverse osmosis method for concentrating organic contaminants, Deinzer et al. (1975) detected phthalic anhydride in tap water from Cincinnati, OH; however, concentrations were not reported. Similarly, Fielding et al. (1981) qualitatively reported the detection of phthalic anhydride in 1 of 14 treated waters in England.

3.2. AIR

Phthalic anhydride is often noted in air because of its low eye irritation threshold (Howard and Durkin, 1973). The major source of phthalic anhydride in air is the process off-gas (Fawcett, 1970). Catalytic oxidation of the off-gas is currently being used to minimize the level of organic pollutants (Conklin et al., 1980); however, phthalic anhydride present in the atmosphere is likely to be converted to phthalic acid. Weschler (1981) reported the presence of phthalic anhydride at a concentration of ~10 ng/m^3 in an arctic aerosol collected in 1979; however, the author noted that phthalic anhydride most likely originated from the partial hydrolysis of phthalate esters followed by dehydration in the GC injection port.

According to the National Occcupational Health Survey (NIOSH, 1985), ~142,660 people are annually exposed to phthalic anhydride from occupational situations.

3.3. FOOD

In the only available report about the detection of phthalic anhydride in food, Coleman et al. (1981) identified but did not quantify phthalic anhydride in the volatile flavor components of baked Idaho potatoes by both MS and IR spectral identification.

3.4. DERMAL

Pertinent data regarding dermal exposure to phthalic anhydride could not be located in the available literature as cited in the Appendix.

3.5. SUMMARY

Phthalic anhydride was identified in effluents from two unspecified chemical plants in the United States (Shackelford and Keith, 1976). It was also detected in several drinking waters in the United States, although no concentrations were reported (Shackelford and Keith, 1976; Kool et al., 1982; Deinzer et al., 1975). It was also identified in 1 of 14 treated water samples in England (Fielding et al., 1981).

The only reported presence of phthalic anhydride in the atmosphere was in an arctic aerosol at a concentration of ~10 mg/m^3 (Weschler, 1981); however, the author noted that phthalic anhydride most likely originated from the partial hydrolysis of phthalate esters followed by dehydration in the GC injection port.

Coleman et al. (1981) detected phthalic anhydride in the volatile flavor components of baked Idaho potatoes by MS and IR spectral identification.

Pertinent data regarding dermal exposure to phthalic anhydride could not be located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

Dixon et al. (1978) reported that covalently bound radioactivity was found in all tissues of fetuses of CD-1 mouse dams injected intraperitoneally with 80 mg/kg ^{14}C-phthalic anhydride on days 11, 12 and 13 of gestation. No other data regarding the pharmacokinetics or metabolism of phthalic anhydride could be located in the available literature as cited in the Appendix.

5. EFFECTS

5.1. CARCINOGENICITY

In an NCI (1979) carcinogenicity bioassay of phthalic anhydride, 50 male and 50 female 6-week-old F344 rats and 50 male and 50 female 6-week-old B6C3F1 mice were treated with 98.8% pure phthalic anhydride in their diets for 2-years. For the rats, the low dose was 7500 ppm and the high dose was 15,000 ppm. Mice were initiated at 25,000 ppm (low dose) or 50,000 ppm (high dose); however, because of severe weight loss, the levels were lowered after 32 weeks to 12,500 and 25,000 ppm for male mice and 6250 and 12,500 ppm for female mice. The TWA dose levels were 16,346 and 32,692 ppm for male mice and 12,019 and 24,038 ppm for female mice. In both species, groups of 20 males and 20 females received the standard diet only and served as controls. Mice were treated for 104 weeks and rats for 105 weeks.

All animals were checked twice daily for deaths, and once daily for signs of toxicity and tumors. Clinical examinations and palpations for masses were made and body weights were measured each month. Necropsies were performed on all animals that died, that were killed when moribund and that survived to the end of the study. Gross and microscopic examinations of all major tissues, organs and lesions were also performed.

For both rats and mice, there were no significant differences in survival among groups and there were sufficient numbers of surviving animals (72-90%) after 2 years for analysis of late-developing tumors. In the female rats, there were two sites that showed group differences with regard to tumor incidences (Table 5-1). The incidences of alveolar/bronchiolar adenoma were 0/20 (controls), 0/50 (low dose) and 5/50 (high dose). These results were statistically significant ($p=0.02$) by the Cochran-Armitage test for linear trend, but not significant in individual comparisons by the

TABLE 5-1

Two-Year Dietary Exposure of 50 Female F344 Rats Treated With 98.8% Phthalic Anhydride[a]

Dose[b] (mg/kg/day)	Target Organ	Tumor Type	Tumor Incidence (p value)
0	alveoli/bronchioli	adenoma	0/20 (p=0.020)[c]
375			0/50
750			5/50
0	hematopoietic system	lymphoma	1/20 (p=0.019)[d]
375			11/50
750			4/50

QUALITY OF EVIDENCE

Strengths of Study: Sufficient number of rats in each experimental group; administration was dietary; two concentration levels (MTD and 1/2 MTD) in two species of rodents; adequate number of animals for analysis of late-developing tumors; comprehensive histological examination

Weakness of Study: Small number of control rats; no hematological or clinical chemistry analyses.

Overall Adequacy: Adequate

[a]Source: NCI, 1979

[b]Calculated according to U.S. EPA (1980) guidelines

[c]Statistically significant dose-related trend by Cochran-Armitage test; Fisher Exact tests for individual comparisons nonsignificant

[d]Statistically significant departure from linear trend; Fisher Exact tests for individual comparisons nonsignificant

Fisher Exact test. There were no treatment-related differences in the incidences of bronchiolar/alveolar carcinoma in female rats, nor any differences in lung tumors in males. The incidences of lymphoma in female rats were 1/20 (controls), 11/50 (low-dose group) and 4/50 (high-dose group). These data indicate a significant (p=0.019) departure from linear trend, and Fisher Exact test results were not significant. The historical incidence of this neoplasia in untreated F344 female rats is 4.9% (NCI, 1979), although an incidence as high as 20% has been observed (NCI, 1979).

NCI (1979) concluded that the evidence for an association between phthalic anhydride and occurrence of lymphomas in the female rats was questionable, based on the nonsignificant results of the Fisher Exact test and on the occasionally high spontaneous rate of lymphomas occurring in historic controls.

There were no positive dose-related trends or significant increases in the incidence of tumors in male rats. There were no treatment-related increased tumor incidences in either male or female mice. The NCI (1979) concluded that phthalic anhydride was not carcinogenic for F344 rats or B6C3F1 mice of either sex under the conditions of the assay.

5.2. MUTAGENICITY

Mutagenicity testing of phthalic anhydride has been limited (Table 5-2). The compound was not mutagenic in Salmonella typhimurium strains TA98, TA100, TA1535 or TA1537, when tested with or without S-9 metabolic activation in a spot test (Florin et al., 1980) or by plate incorporation (Zeiger et al., 1985). Shelby and Stasiewicz (1984) summarized results of the NTP testing program for in vitro genetic toxicity. Phthalic anhydride was not genotoxic in a Salmonella reverse mutation assay or in studies of mammalian cell chromosome aberrations or sister chromatid exchange. No other details were provided.

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TABLE 5-2

Mutagenicity Testing of Phthalic Anhydride

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium strains TA98, TA100, TA1535, TA1537	dissolved in EtOH	spot test	3 µmol/plate	±S-9	-	Also negative in TA100 on quantitative test up to 3 µmol/plate	Florin et al., 1980
Reverse mutation	S. typhimurium strains TA98, TA100, TA1535, TA1537	99+% in DMSO	plate incorporation	1-666 µg/plate	±S-9	-	Positive controls used with each strain	Zeiger et al., 1985

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5.3. TERATOGENICITY

Pertinent data regarding teratogenicity after oral or inhalation exposure to phthalic anhydride could not be located in the available literature as cited in the Appendix. A series of abstracts (Dixon et al., 1978; Brown et al., 1978; Fabro et al., 1977) and a single published study (Fabro et al., 1982) described the teratogenic potential of phthalic anhydride and related compounds. The primary endpoint reported is dysmorphogenesis. However, these studies have briefly described the effects of intraperitoneal administration of phthalic anhydride on gestation days 8-10 or 11-13 in CD-1 mice. The minimum dose needed to produce fetal abnormalities was 55.5 mg/kg on days 11, 12 and 13 of gestation (Brown et al., 1978). Fabro et al. (1977) noted that 80 mg/kg phthalic anhydride on days 8, 9 and 10 led primarily to rib and vertebral malformations in 25.6% of the fetuses. Cleft palate predominated after treatment on days 11-13 (Dixon et al., 1978). Fabro et al. (1982) cited an intraperitoneal tD_{50} of ~203 mg/kg/day in gravid CD-1 mice treated on days 8-10 of gestation. In 50% of the fetuses this dose produced major malformations, which included malformations other than undescended testes, extra lung lobes or minor skeletal aberrations. Since the intraperitoneal LD_{50} (75.5 mg/kg) in adult female mice from the Fabro et al. (1982) study was considerably less than reported values of oral LD_{50}s (Section 5.6.), extrapolation from intraperitoneal to oral dose values is difficult.

Korhonen et al. (1983) found phthalic anhydride to be embryotoxic in chicken eggs, with an ED_{50} of 56 µg/egg.

5.4. OTHER REPRODUCTIVE EFFECTS

An abstract of a Russian study (Protsenko, 1970) reported that chronic inhalation of 1 mg/m³ phthalic anhydride decreased the content of ascorbic, dehydroascorbic and nucleic acids in the seminiferous tubules of

male rats and impaired reproductive performance. At 0.2 mg/m³, ascorbic and dehydroascorbic acid levels were decreased and reproductive performance was also impaired. Decreases in the amount of dehydroascorbic acid were also noted at 0.02 mg/m³. Additional details regarding length of exposure and magnitude of effects were not given.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

In the only animal study available of the long-term toxicity of orally administered phthalic anhydride, NCI (1979) exposed groups of 50 male and 50 female F344 rats and 50 male and 50 female B6C3F1 mice to dietary phthalic anhydride for 2 years (see Section 5.1.). Rats were given doses of either 7500 or 15,000 ppm. TWA concentrations for mice were 16,346 and 32,694 ppm (males), and 12,019 and 24,038 ppm (females). Twenty animals of each species and sex were fed the basal diet only and served as controls. All animals were observed for clinical signs, weighed monthly and palpated for masses. Necropsies and comprehensive histopathological examinations were performed on all animals that died spontaneously or were sacrificed, unless precluded by autolysis.

In male rats, the mean body weights of the high-dose group were lower than control weights from week 13 to the end of the study, but this decrease was never >10%. Treated rats had low incidences of arched back, rough hair coat, ulceration and corneal opacity, effects not observed in controls. No other treatment-related nonneoplastic effects were reported, and the treated rats lived as long or longer than the controls.

Treatment did not alter the survival rates of either sex of mice, relative to controls; however, the levels used caused a dose-related inhibition of weight gain. By the end of the study, the inhibitions in weight gain for male mice were ~12% at the low dose and ~25% at the high dose, compared with controls. For the females, the respective values were ~12%

and ~27%. There were no treatment-related differences in clinical signs or tissue masses. The NCI (1979) stated that there were no treatment-related differences in chronic inflammatory, degenerative or proliferative lesions in either sex; however, examination of the incidence data for nonneoplastic lesions revealed increased incidences of several lesions (Table 5-3). Exposed females and males had a greater frequency of kidney and lung lymphocytosis than did untreated controls. The incidence of chronic bile duct inflammation was significantly increased in high-dose males and females. Adrenal cortical atrophy and mineralization of the thalamus occurred in males at dose-related significantly increased incidences.

In order to determine the MTD for use in the chronic study, the NCI (1979) conducted a 7-week dietary study on rats and mice of both sexes. Groups of five male and five female rats and five male and five female mice were given either 0, 6200, 12,500, 25,000 or 50,000 ppm phthalic anhydride for 7 weeks followed by a 1-week observation period. Each animal was weighed twice weekly, and histopathological examinations were performed on all animals. The NCI (1979) found dose-related inhibitions in weight gain in both sexes of rats. At week 7, male rats given 50,000 ppm showed an inhibition of 26% and females an inhibition of 24%, relative to controls. At all four concentrations, treated mice showed no decreases in weight gain, compared with controls. In rats given 25,000 ppm, four males had slight centrilobular cytoplasmic vacuolation in the liver. There were no other lesions observed in either species in any treatment group, and no animals died during this testing.

An abstract of a Polish study (Sagan, 1973) described the fate of 810 workers occupationally exposed for ~12 years to phthalic anhydride. The compound was shown to be an irritant of mucous membranes, and to increase susceptibility toward diseases of the digestive and respiratory tracts.

TABLE 5-3

Incidence of Nonneoplastic Lesions in B6C3f1 Mice Treated with Phthalic Anhydride in the Diet for 2 Years[a,b]

Tissue, Lesion	Females			Males		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Lung, lymphocytosis	2/20	32/49 (p<0.001)	34/48 (p<0.001)	6/20	19/50 (NS)	30/45 (p=0.007)
Kidney, lymphocytosis	0/19	22/48 (p<0.001)	26/48 (p<0.001)	0/20	15/50 (p=0.003)	37/49 (p=0.008)
Bile duct, chronic inflammation	10/20	30/48 (NS)	36/48 (p=0.04)	1/20	7/50 (NS)	17/49 (p=0.008)
Adrenal cortex, atrophy	16/28	37/46 (NS)	42/48 (NS)	0/19	23/49 (p<0.001)	40/48 (p<0.001)
Thalamus, mineralization	8/20	20/49 (NS)	26/48 (NS)	0/19	18/50 (p=0.001)	23/49 (p<0.001)

[a]Source: NCI, 1979

[b]Fisher Exact test performed at SRC

NS = Not stated

Markman and Savinkina (1964) observed respiratory damage in phthalic anhydride workers exposed for ≥2 years and pulmonary fibrosis in those exposed for 6 years. No other details were provided.

Ohta et al. (1979) conducted a retrospective study of factory workers exposed to phthalic anhydride during the polymerization processing of alkyd resins. After exposure to air concentrations of ~24.9-77.3 (151-468 mg/m³) ppm phthalic anhydride before 1968, a male worker suffered from sneezing, sore throat, urticarial exanthema and conjunctival hyperemia; 3 years later, dyspnea developed. Subsequently, in 1968, air concentrations in the factory were decreased; the levels in the factory air were either nondetectable or 1.1 ppm (6.7 mg/m³). A survey of 20 exposed workers in 1971 revealed that incidences of respiratory and eye symptoms in individuals hired before 1968, when levels in the plant ranged from 24.9-77.3 ppm (151-468 mg/m³), were higher than those hired after levels in air were decreased and higher than those among three control groups. Results of a 1976 survey showed that incidences of respiratory and eye symptoms reported by exposed workers were almost the same as those in three control groups of unexposed workers, suggesting that the effects may be reversible. There were also no changes in pulmonary function that were due to phthalic anhydride exposure, compared with the three control groups.

Gilioli et al. (1978) studied the neuromuscular reactions of six workers exposed to phthalic anhydride during the acid-catalyzed formation of phthalate ester from phthalic anhydride and alcohol. The workers were employed for an average of 6.6 years. Average concentrations of phthalate esters ranged from <1-5 mg/m³ in some areas and 5-60 mg/m³ in other areas; the authors did not specify phthalic anhydride concentrations. Most subjects showed normal responses in a variety of neurological tests, including

electromyography, nerve conduction velocity (both ulnar and sciatic) and tests of hand and feet hypoextension; however, one subject had bilateral Achilles hyporeflexia.

5.6. OTHER RELEVANT INFORMATION

Sax (1984) listed oral LD_{50}s for phthalic anhydride of 4020 mg/kg in rats and 2000 mg/kg in mice. Zhilova and Kasparov (1968) stated that, unlike effects seen by other routes, oral exposure has no deleterious effects on the mucous membranes of the skin, eyes or respiratory tract. Fabro et al. (1982) reported an intraperitoneal LD_{50} of 75.5 mg/kg in female mice .

Maccia et al. (1976) and Fawcett et al. (1977) reported cases in which exposure to heavy concentrations of phthalic anhydride dust induced hypersensitivity and bronchial asthma in humans. These results were confirmed and extended in other individual case studies (Chester et al., 1977; Levy et al., 1978; Ward and Davies, 1983). Maccia et al. (1976) also identified a phthalic anhydride-specific IgE. Bernstein et al. (1982), using both enzyme-linked immunosorbent and radioimmunoassays, found elevated levels of binding to both total antibodies and specific IgG and IgE in workers in the heavy exposure group concurrently sensitized to phthalic and trimetallic anhydrides. In this case study the exposure group consisted of workers in the laboratory and plants whereas the low exposure group included supervisors, engineers and shipping/receiving employees. Bernstein et al. (1984) observed a correlation in reaginic antibody binding and occupational asthma in four workers exposed to phthalic, hexahydrophthalic or himic anhydride powder.

Sensitization to phthalic anhydride at 0.1% concentration has been found in guinea pigs after intracutaneous (Jacobs et al., 1940) and inhalation (Chernichenko et al., 1973) exposure.

SUMMARY

The NCI (1979) found phthalic anhydride to be noncarcinogenic based upon year bioassay in which F344 rats and B6C3F1 mice were exposed to dietary ls up to 15,000 ppm (rats) or 33,000 ppm (mice).

Phthalic anhydride was negative for revere mutations in several strains Salmonella typhimurium mutation assays with or without metabolic activa- (Florin et al., 1980; Zeiger et al., 1985; Shelby and Stasiewicz, 1984) for chromosome aberrations or sister chromatid exchanges in mammalian culture (Shelby and Stasiewicz, 1984). Intraperitoneal injections in id mice, at doses as low as 55.5 mg/kg, have been reported to produce l abnormalities (Brown et al., 1978). An intraperitoneal dose of ~203 g/day on gestation days 8-10 in CD-1 mice produced major, but unspeci- , malformations in 50% of all fetuses (Fabro et al., 1982). Korhonen et (1983) found phthalic anhydride to be embryotoxic in chicken eggs. senko (1970) cited reproductive defects in rats exposed to as little as mg/m³ phthalic anhydride.

In the NCI (1979) bioassay, male rats exposed to 15,000 ppm dietary alic anhydride for 2 years showed a minor inhibition in weight gain, tive to untreated controls. Treated rats of both sexes also had low dences of arched back, rough hair coat, ulceration and corneal opacity, ough it was unclear if these effects were treatment-related. Treatment ale mice with 16,346 or 32,694 ppm and of female mice with 12,019 or 038 ppm led to more severe and concentration-related inhibitions in ght gain. Low- or high-dose female and male mice had significantly reased incidences of lung and kidney lymphocytosis. High-dose male and ale mice had significantly increased incidences of chronic bile duct flammation, and low- and high-dose male had dose-related significantly creased incidences of adrenal atrophy and mineralization of the thalamus.

In a 7-week study designed to determine an MTD for the chronic experiment, the NCI (1979) noted severe inhibition in weight gain in male and female rats given 50,000 ppm phthalic anhydride, and hepatocytic cytoplasmic vacuolation in male rats fed 25,000 ppm. At 50,000 ppm, hepatic toxicity was not found in either rats or mice.

Studies of occupational exposure to phthalic anhydride powder have revealed asthmatic attacks and mucous membrane irritation of the eyes, lungs and skin (Markman and Savinkina, 1964; Ohta et al., 1979). Ohta et al. (1979) reported that factory workers exposed to air concentrations of phthalic anhydride dust ranging from 24.9-77.3 ppm (151-468 mg/m^3) had higher incidences of respiratory and eye symptoms than workers exposed to $\leq$1.1 ppm (6.7 mg/m^3). In six workers employed an average of 6.6 years in a phthalic anhydride plant, normal neuromuscular activity was observed, with the exception of one worker who suffered from a bilateral Achilles hyporeflexia (Gilioli et al., 1978). The asthma-inducing and hypersensitivity characteristics of phthalic anhydride have been determined by a number of investigators (Maccia et al., 1976; Fawcett et al., 1977; Bernstein et al., 1982, 1984), who have observed specific antibody binding against the compound.

Sensitization to phthalic anhydride has also been demonstrated in experimental animals (Jacobs et al., 1940; Chernichenko et al., 1973). Zhilova and Kasparov (1968) stated, however, that oral exposure did not induce the sensitizing and irritancy effects observed after other routes of exposure.

6. AQUATIC TOXICITY

6.1. ACUTE

Pickering and Henderson (1966) found that the 96-hour LC_{50} of phthalic anhydride in the fathead minnow, Pimephales promelas, was >50 mg/ℓ. Applegate et al. (1957) reported that sea lampreys, Petromyzon marinius were unaffected by exposure to 5 mg/ℓ for 24 hours.

6.2. CHRONIC

Pertinent data regarding chronic toxicity of phthalic anhydride to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Pertinent data regarding the effects of phthalic anhydride on aquatic plants could not be located in the available literature as cited in the Appendix.

6.4. RESIDUES

There were two studies available in which laboratory microecosystems consisting of plants, invertebrates and fish were exposed to radiolabeled phthalate compounds (Lu and Metcalf, 1975; Soedergren, 1982). In the study by Lu and Metcalf (1975), organisms were exposed to 0.016 mg/ℓ phthalic anhydride in water. The alga Oedogonium sp. accumulated phthalic anhydride residues of 2.027 µg/g. Mosquitos, Culex pipiens, snails, Physa sp., Daphnia sp., and mosquitofish, Gambusia affinus, contained negligible levels of phthalic anhydride. Phthalic anhydride degradation consisted of decarboxylation and benzoic acid degradation and most of the radioactivity in all organisms was found in conjugated forms. The authors concluded that phthalic anhydride was not subject to significant ecological magnification.

In a similar study by Soedergren (1982), a laboratory microecosystem was exposed to radiolabeled di-2-ethylhexyl phthalate at an initial concentration of 1-2 mg/ℓ, which declined to 0.001 mg/ℓ after 28 days. The levels of phthalic anhydride (expressed as mg/kg as di-2-ethylhexyl phthalate equivalents), a di-2-ethylhexyl phthalate metabolite, in the various species were as follows: plant, Chara chara 4.46; plant, Mentha aquatica 3.66; amphipod, Gammarus pulex 0.49; caddisfly, Limnephilus sp. 18.99; leech, Helobdella sp. 0.88; flatworm, Dendrocoelum lacteum 0.21; and lamprey, Lampetra planeri 0.56.

6.5. SUMMARY

Little information is available concerning the toxicity of phthalic anhydride to aquatic organisms. Fathead minnows and sea lampreys were unaffected by acute exposures to 56 and 5 mg/ℓ, respectively (Applegate et al., 1957; Pickering and Henderson, 1966). Two laboratory microecosystem studies (Lu and Metcalf, 1975; Soedergren, 1982) indicated that phthalic anhydride was not accumulated to a great extent in organisms exposed to phthalic anhydride itself or di-2-ethylhexyl phthalate.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

OSHA (1985) has established a workplace regulation of 2 ppm (12 mg/m^3) for phthalic anhydride as an 8-hour TWA (Permissible Exposure Limit). The ACGIH (1986) recommended a TLV of 1 ppm (6 mg/m^3), based upon the irritant properties of phthalic anhydride. The compound has been shown to have a lower degree of irritancy than maleic anhydride, which has a TLV of 0.25 ppm. The ACGIH (1985-1986) adopted the TLV of 1 ppm.

7.2. AQUATIC

Guidelines or standards for the protection of aquatic organisms from phthalic anhydride could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

The NCI (1979) found phthalic anhydride to be noncarcinogenic, based upon a 2-year bioassay in F344 rats and B6C3F1 mice exposed to dietary levels up to 15,000 ppm (rats and 33,000 ppm (mice).

Phthalic anhydride was negative for reverse mutations in several strains of Salmonella typhimurium with and without metabolic activation (Florin et al., 1980; Zeiger et al., 1985; Shelby and Stasiewicz, 1984) and for chromosome aberrations and sister chromatid exchange in mammalian cell culture (Shelby and Stasiewicz, 1984). Intraperitoneal injections in gravid CD-1 mice, at doses as low as 55.5 mg/kg, have been reported to produce fetal abnormalities (Brown et al., 1978). An intraperitoneal dose of ~203 mg/kg/day on gestation days 8-10 in CD-1 mice produced major, but unspecified, malformations in 50% of all fetuses (Fabro et al., 1982). The teratogenicity of phthalic anhydride has not been studied by the oral route. Korhonen et al. (1983) found phthalic anhydride to be embryotoxic in chicken eggs. Protsenko (1970) cited reproductive defects in rats exposed to as little as 0.2 mg/m³ phthalic anhydride.

In the NCI (1979) bioassay, male rats exposed to 15,000 ppm dietary phthalic anhydride for 2 years showed a minor inhibition in weight gain, relative to untreated controls. Treated rats of both sexes also had low incidences of arched back, rough hair coat, ulceration and corneal opacity, although it was unclear if these effects were concentrated-related. Treatment of male mice with 16,346 or 32,694 ppm and of female mice with 12,019 or 24,038 ppm led to more severe and concentration-related inhibitions in weight gain. Low- and high-dose female and male mice had significantly increased incidences of lung and kidney lymphocytosis. High-dose male and

female mice had significantly increased incidences of chronic bile duct inflammation and low- and high-dose male mice had dose-related significantly increased incidences of adrenal atrophy and mineralization of the thalamus. In a 7-week study designed to determine an MTD for the chronic experiment, the NCI (1979) noted severe inhibition in weight gain in male and female rats given 50,000 ppm phthalic anhydride, and hepatocytic cytoplasmic vacuolization in male rats fed 25,000 ppm. At 50,000 ppm, hepatic toxicity was not found in either rats or mice.

Studies of occupational exposure to phthalic anhydride powder have revealed asthmatic attacks and mucous membrane irritation of the eyes, lungs and skin (Markman and Savinkina, 1964; Ohta et al., 1979; Gilioli et al., 1978). Ohta et al. (1979) reported that factory workers exposed to air concentrations of phthalic anhydride dust ranging from 24.9-77.3 ppm (151-468 mg/m^3) had higher incidences of respiratory and eye symptoms than workers exposed to $\leq$1.1 ppm. In six workers employed an average of 6.6 years in a phthalic anhydride plant, normal neuromuscular activity was observed, with the exception of one worker who suffered from a bilateral Achilles hyporeflexia (Gilioli et al., 1978). The asthma-inducing and hypersensitivity characteristics of phthalic anhydride have been determined by a number of investigators (Maccia et al., 1976; Fawcett et al., 1977; Bernstein et al., 1982, 1984), who have observed specific antibody binding against the compound.

Sensitization to phthalic anhydride has also been demonstrated in experimental animals (Jacobs et al., 1940; Chernichenko et al., 1973). Zhilova and Kasparov (1968) stated, however, that oral exposure did not induce the sensitizing and irritancy effects observed after other routes of exposure.

Since phthalic anhydride is considered to be noncarcinogenic and results of mutagenicity testing were negative, an RfD should be calculated from the available oral chronic toxicity data.

The human occupational exposure data (Sagan, 1973; Ohta et al., 1979; Gilioli et al., 1978) suggest that phthalic anhydride powder is a mucous membrane irritant and sensitizer. Although exposure levels were well characterized in the Ohta et al. (1979) study, Zhilova and Kasparov (1968) reported that inhalation exposure leads to a sensitizing reaction not observed after oral administration; therefore, extrapolation from occupational data may be tenuous at best.

In the NCI (1979) study, the dietary level of 7500 ppm resulted in low incidences of possibly age-related clinical effects in rats. At the 15,000 ppm level, male rats had slightly (<10%) reduced body weight gain, and male and female rats had low incidences of the clinical effects. Although these clinical effects may have represented an acceleration of an age-related process, they were not considered adverse because low- and high-dose rats survived as long or longer than controls. The slightly reduced body weight gain of the male rats at the 15,000 ppm level could be considered a NOAEL. This dose was transformed to a dose of 750 mg/kg/day by multiplying by a food consumption factor of 0.05. Survival of the high-dose rats was greater than that of controls. Furthermore, the reduced body weight gain may have been the result of food refusal at the high dietary level; NCI (1979) did not report food consumption data. Male and female mice (NCI, 1979) had a dose-related decreased body weight gain at high dietary levels (12,019-32,692 ppm); however, male and female mice also had dose-related significantly increased incidences and dose-related increased severity of histopathological lesions. The lowest dietary level of 12,019 ppm in mice is

equivalent to 1562 mg/kg/day (assuming a mouse eats a daily amount of food equal to 13% of its body weight), which probably represents the LOAEL. Thus, the 750 mg/kg/day transformed dose for rats is the highest NOAEL. Dividing 750 mg/kg/day by an uncertainty factor of 100 results in an RfD of 7.5 mg/kg/day. The provisional RfD of 7.5 mg/kg/day or 525 mg/kg/day for a 70 kg human is recommended.

Phthalic anhydride was associated with teratogenic effects in the offspring of mice injected intraperitoneally with $\geq$55.5 mg/kg during organogenesis (Brown et al., 1978; Fabro et al., 1982; Dixon et al., 1978). Because the teratogenicity of phthalic anhydride has not been studied by the oral route, and because absorption and comparative metabolism data for the oral and intraperitoneal routes were not available, it is not known if the provisional RfD for oral exposure will be protective against possible teratogenic effects or reproductive performances in male subjects.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Studies of the chronic toxicity of phthalic anhydride were discussed in Section 5.5. and are summarized in Table 9-1.

As seen from Table 9-1, the most severe effects of phthalic anhydride exposure are the bronchial asthma and other respiratory effects found in humans as a result of occupational exposure to $\geq$151 mg/m^3 in the study by Ohta et al. (1979). These findings are supported by other case reports of bronchial asthma as a result of occupational exposure to phthalic anhydride (Maccia et al., 1976; Fawcett et al., 1977; Chester et al., 1977; Levy et al., 1978; Ward and Davies, 1983), but exposure levels were not quantitated. Since bronchial asthma represents a definitive organ dysfunction, it warrants an RV_e of 8. The exposure level of 151 mg/m^3 is equivalent to a dose of 15.4 mg/kg/day (see Table 9-1), which when multiplied by 70 kg results in an MED of 1078 mg/day. The MED corresponds to an RV_d of 1. Multiplying the RV_d by the RV_e results in a CS of 8, which corresponds to an RQ of 1000 (Table 9-2).

Less serious effects occurred at higher equivalent doses in rats and mice (see Table 9-1). Since these data would result in lower RV_ds and RV_es, CSs need not be calculated. Therefore, the RQ for phthalic anhydride is based on the occupational exposure-induced bronchial asthma (Table 9-3).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The only study that adequately addressed the issue of the carcinogenicity of phthalic anhydride was the 2-year oral bioassay by the NCI (1979) (see Section 5.1. and Table 5-1). There was a significant (0.020) dose-related trend for the increased incidence of alveolar/bronchiolar adenoma in

TABLE 9-1

Toxicity Summary for Phthalic Anhydride

Route	Species/ Strain	Sex	Number at Start	Average Weight[a] (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed[b] Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
Oral	rat/F344	M/F	50/sex/ group	0.39 (M) 0.22 (F)	diet	98.8%	15,000 ppm 105 weeks	750	133[c] (M)	Slightly decreased body weight gain in males	NCI, 1979
Oral	mice/ B6C3F1	M	50/group	0.034 (high dose) 0.040 (low dose)	diet	98.8%	16,346 and 32,692 ppm[d] 104 weeks	2125 and 4250	176 and 334[c]	Lymphocytosis (high dose); adrenal cortex atrophy high and low; bile duct inflammation (high); mineralization of the thalamus (low and high); inhibition in weight gain (low and high)	NCI, 1979
Oral	mice/ B6C3F1	F	50/group	0.030 (high dose) 0.036 (low dose)	diet	98.8%	12,019 and 24,038 ppm[d] 104 weeks	1562 and 3125	125 and 236[c]	Kidney and lung lymphocytosis; inhibition in weight gain (low and high dose); bile duct inflammation (high dose)	NCI, 1979
Inhalation	human	NR	20/group	70[e]	powder	NA	24.9-77.3 ppm (151-468 mg/m³) occupational		15.4-47.8[f]	Bronchial asthma	Ohta et al., 1979

[a]As estimated from growth curves

[b]As calculated from U.S. EPA (1980) guidelines

[c]Calculated by multiplying the transformed animal dose by the cube root of the ratio of the average animal body weight to the reference human body weight (70 kg)

[d]TWA concentrations

[e]Reference body weight (U.S. EPA, 1980)

[f]Calculated by multiplying the exposure by 5/7 and by 10 m³/day (human breathing volume in an 8-hour day) and dividing by 70 kg

NA = Not applicable; NR = not reported

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TABLE 9-2

Composite Score for Phthalic Anhydride

Route	Species	Dose	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Inhalation (occupational)	human	151 mg/m³	1078	1	bronchial asthma	8	8	1000	Ohta et al., 1979

TABLE 9-3

Phthalic Anhydride

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	1078 mg/day
Effect:	bronchial asthma
Reference:	Ohta et al., 1979
RV_d:	1
RV_e:	8
Composite Score:	8
RQ:	1000

*Equivalent human dose

female rats; however, the incidence was not significantly different compared with controls. Higher incidences of lymphoma occurred in low- and high-dose female rats than in controls; however, the differences were not significant. Furthermore, the increase was not significantly dose-related; rather there was a significant ($p=0.019$) departure from linearity. No increased tumor incidences were found in male rats or male and female mice. NCI (1979) concluded that under the conditions of the bioassay, phthalic anhydride was not carcinogenic for F344 rats or B6C3F1 mice.

Because of these negative results, a potency factor for phthalic anhydride cannot be calculated. The compound should be categorized in IARC Group 3, and in CAG Group E (U.S. EPA, 1984). Therefore, criteria other than carcinogenicity must be used for ranking phthalic anhydride for a reportable quantity under CERCLA. When additional data for carcinogenicity or genotoxicity become available, the weight of evidence classification of Group E will be reconsidered.

10. REFERENCES

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

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In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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